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SYNTHESIS OF SOME *C*-GLYCOSYL- AND POLYHYDROXYALKYL-PYRIDAZINES

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ABSTRACT

Photo-oxygenation of 3-hydroxymethyl-5-(2,3-*O*-isopropylidene-β-D-erythrofuranosyl)-2-methylfuran, 5-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-3-(1-hydroxyethyl)-2-methylfuran (**8a**), and 2-methyl-5-(1,2,3,4-tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl)-3-furoic acid (**8b**) yielded the corresponding *endo*-peroxides, which were transformed into 4-hydroxymethyl-6-(2,3-*O*-isopropylidene-β-D-erythrofuranosyl)-3-methylpyridazine, 6-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-4-(1-hydroxyethyl)-3-methylpyridazine, and 6-(D-*arabino*-tetritol-1-yl)-3-methylpyridazine by treatment with hydrazine. The γ-diketones (*Z*)-1-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-3-(1-hydroxyethyl)pent-2-ene-1,4-dione and D-*arabino*-6,7,8,9-tetraacetoxy-4-methoxynonane-2,5-dione can be obtained by reduction of the *endo*-peroxides **9a** and **9b** (derived from **8a** and **8b**, respectively) with dimethyl sulphide. The C → O rearrangement reported for *C*-glycosyl *endo*-peroxides[1] was also observed for **9a**.

RESULTS AND DISCUSSION

Photo-oxygenation of *C*-glycosylfurans provides a route to *C*-glycosyl derivatives of unsaturated γ-diketones[1]. We now report on the reaction of some of these compounds with hydrazine to give *C*-glycosylpyridazine derivatives.

The photo-oxygenation of 3-hydroxymethyl-5-(2,3-*O*-isopropylidene-β-D-erythrofuranosyl)-2-methylfuran[1] (**1**) was carried out as previously reported. Reduction of the resulting hydroperoxide with dimethyl sulphide was monitored by ^{1}H-n.m.r. spectroscopy (see Experimental). However, with sufficient hydrazine, reduction to **2** and subsequent transformation into the pyridazine derivative **3** could be effected. A similar sequence of reactions (photo-oxygenation, reduction, and cyclisation) was used for the synthesis of polyhydroxyalkylpyridazine derivatives.

Acetonation of 3-acetyl-5-(D-*arabino*-tetritol-1-yl)-2-methylfuran[2] (**4**) yielded 3-acetyl-5-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-2-methylfuran (**5**), 3-acetyl-5-(2,3-*O*-isopropylidene-β-D-erythrofuranosyl)-2-methylfuran (**6**), and its α anomer (**7**). The n.m.r. signals for the isopropylidene methyl groups of **6** and **7** accord with the Imbach rule[3] for the *arabino* and *ribo* analogues. The re-

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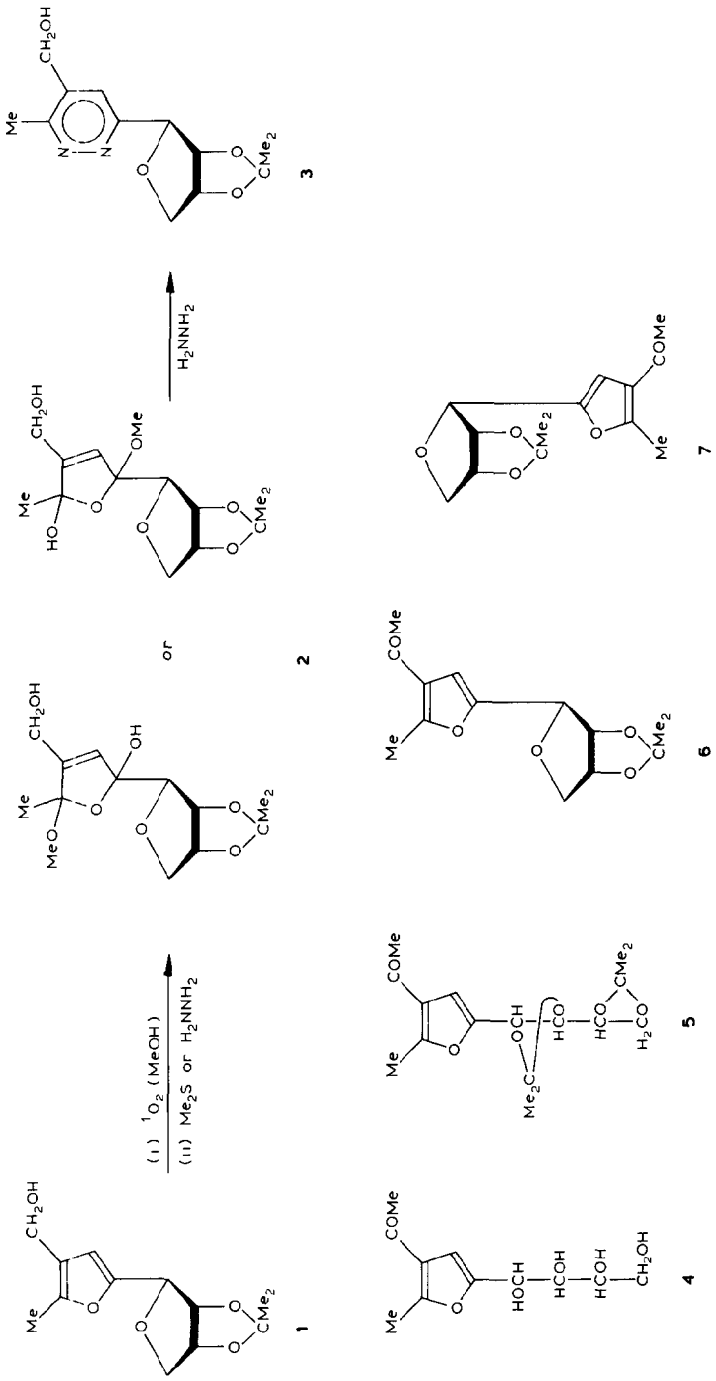
(i) $^1O_2$ (MeOH)
(ii) Me_2S or H_2NNH_2
H_2NNH_2
or

Series	R	R′
a		CHOH—Me
b		COOH (8,9) H (10)
c		H
d		CHOH—Me

10 ab

12 ac
13 d

16 b

9 a b

or

11 a

15 a

8 a b

14 a

lative yields of **5–7** depended on the reaction conditions. When sulfuric acid and copper sulfate were used, **5** was the main product; in the absence of copper sulfate, **6** was the main product.

Reduction of **5** with lithium aluminium hydride gave the corresponding alcohol **8a**, photo-oxygenation of which in methanol yielded the hydroperoxide **11a** having ^{1}H-n.m.r. signals at δ 1.55 (Me-C$<^{O}_{O}$) and 3.15–3.30 (OMe) corresponding to different isomers. Compound **11a** oxidised dimethyl sulphide to dimethyl sulfoxide, and the resulting diketone **10a** showed a singlet at δ 2.30 for Me-CO. Reaction of the product of photo-oxygenation of **8a** with methanolic hydrazine yielded the pyridazine **12a**, the structure of which was established by the usual methods (see Experimental). To increase the water solubility with the aim of possible biological tests, the isopropylidene group was removed from **12a** by acid hydrolysis, yielding the corresponding tetrahydroxyalkylpyridazine **13d**.

All derivatives of *C*-glycosylfurans previously photo-oxygenated[1] had the hydroxyl groups acetalated and an ester or alcoholic substituent at position 3 of the furan nucleus. Compound **8b**[4] (R′ = COOH) has the hydroxyl groups acetylated and a free carboxyl at position 3. The photo-oxygenation of **8b** in methanol was followed by the rapid addition at low temperature of dimethyl sulphide to reduce the resulting *endo*-peroxide, thereby avoiding a possible rearrangement[1]. The reduction was followed by the addition of methanol to the double bond and decarboxylation of the expected β-ketoacid to yield the crystalline γ-diketone **16b** which, with hydrazine in ethanol, gave the pyridazine **12c**.

Photo-oxygenation of **8a** in acetone gave a crude product which contained the *endo*-peroxide **9a**, as indicated by the ^{1}H-n.m.r. signals at δ 1.80 (Me-C$<^{O}_{O}{}^{O}$) and 6.65 (vinylic proton). Rearrangement of **9a** occurred during 12 h at room temperature in a manner similar to that reported for the products of photo-oxygenation of other glycosylfurans[1]. The resulting glycosidic ester **14a** could be hydrolysed with acid to yield the expected lactone, isolated as the derivative **15a** after reaction with methanol, together with D-erythrose, characterised as the osazone after reaction with phenylhydrazine[5].

3-Hydroxymethyl-5-(2,3-*O*-isopropylidene-β-D-erythrofuranosyl)-2-methylfuran (**1**) 5-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-3-(1-hydroxyethyl)-2-methylfuran (**8a**), 2-methyl-5-(1,2,3,4-tetra-*O*-acetyl-D-*arabino*-tetritol-1-yl)-3-furoic acid (**8b**) were treated with hydrazine after photo-oxygenation to yield the corresponding pyridazines **3, 12a,** and **12c**[6].

EXPERIMENTAL

General. — Melting points were determined with an Electrothermal melting-point apparatus and are uncorrected. I.r. spectra were recorded with a Pye Unicam SP 1000 spectrometer. N.m.r. spectra (internal Me_4Si) were recorded with Perkin–Elmer R-20B (^{1}H) and Bruker WP 80 SY spectrometers (^{13}C). Optical rotations were measured with a Perkin–Elmer 141 polarimeter. Elemental analyses were

performed with a Carlo Erba Strumentazione Analyzer 1106. Satisfactory analyses could not be obtained for the non-crystalline compounds described below. The structures assigned accorded with the n.m.r. data. T.l.c. was performed on Silica Gel G (Merck), and column chromatography on Silica Gel 60 Merck (70–230 mesh, ASTM).

Photo-oxygenations were performed at 0° by illumination of solutions also containing 0.01% of Methylene Blue with a Tunsgram Halogen 60000 T8 R7-s-15 lamp. Reactions were monitored by measuring the volume of oxygen consumed.

*Photo-oxygenation of 3-hydroxymethyl-5-(2,3-*O*-isopropylidene-β-*D*-erythrofuranosyl)-2-methylfuran* (**1**). — A solution of **1**[1] (2.03 g, 8 mmol) in ethanol (40 mL) was photo-oxygenated for 30 min under the general conditions. An aliquot (1 mL) of the solution was treated with dimethyl sulphide and concentrated *in vacuo* at room temperature. The ^{1}H-n.m.r. spectrum indicated a mixture of dimethyl sulfoxide [δ 2.52 (s, 6 H)] and **2** [δ 3.22 (OMe), 7.21 (vinylic H)]. The main bulk of the solution was treated with hydrazine (2 g, 62 mmol) and, after 12 h at room temperature, the solution was boiled under reflux for 6 h and then concentrated *in vacuo*. The residue was purified by column chromatography (ether–hexane, 2:1), and then crystallised from ethanol to yield 4-hydroxymethyl-6-(2,3-*O*-isopropylidene-β-D-erythrofuranosyl)-3-methylpyridazine (**3**; 0.85 g, 36%), m.p. 122–123°, $[\alpha]_D^{20}$ −69.5° (*c* 1, chloroform); ν_{max}^{KBr} 3420, 3170, 2860, 1625, 1600, 1380, and 1050 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 1.25 and 1.40 (2 s, 6 H, CMe_2), 2.41 (s, 3 H, Me-3), 3.45–3.93 (m, 2 H, H-4′,4′), 4.46 (d, 2 H, *J* 5 Hz, CH_2OH), 4.66–4.83 (m, 1 H, H-3′), 5.05–5.25 (m, 2 H, H-1′,2′), 5.34 (t, 1 H, *J* 5 Hz, exchangeable with D_2O, CH_2OH), and 7.50 (s, 1 H, H-5).

Anal. Calc. for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.20; H, 6.83; N, 10.45.

*Acetonation of 3-acetyl-5-(*D-arabino-*tetritol-1-yl)-2-methylfuran* (**4**). — A solution of **4**[2] (1 g, 4 mmol) in anhydrous acetone (60 mL) was shaken with anhydrous copper sulfate (2 g) and sulfuric acid (0.2 mL) for 48 h at room temperature, filtered, neutralised (K_2CO_3), and concentrated *in vacuo*. The resulting syrup (1 g, 77%) was purified by column chromatography (ether–hexane, 3:2) to yield 3-acetyl-5-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-2-methylfuran (**5**) as a colorless oil, $[\alpha]_D^{20}$ +13° (*c* 1, chloroform); ν_{max}^{film} 3040, 2990, 1700, 1590, 1390, 1240, 1090, 960, and 860 cm^{-1}. ^{1}H-N.m.r. data (CCl_4): δ 1.22, 1.25, and 1.30 (3 s, 12 H, 2 CMe_2), 2.3 (s, 3 H, Me-2), 2.55 (s, 3 H, COMe), 3.7–4.3 (m, 4 H, H-2′,3′,4′,4′), 4.60–5.0 (m, 1 H, H-1′), and 6.55 (s, 1 H, H-4).

*5-(1,2:3,4-Di-*O*-isopropylidene-*D-arabino-*tetritol-1-yl)-3-(1-hydroxyethyl)-2-methylfuran* (**8a**). — A solution of **5** (4.2 g, 12.9 mmol) in anhydrous ether (25 mL) was added gradually to a suspension of $LiAlH_4$ (630 mg, 16.5 mmol) in ether (40 mL). The mixture was kept for 24 h at room temperature, the excess of reductant was then decomposed by the gradual addition of water (30 mL), and the aqueous layer was removed and extracted several times with ether. The combined extracts were dried (Na_2SO_4) and concentrated to yield **8a** (3.68 g, 87%) as a color-

less oil, $[\alpha]_D^{20}$ +31° (*c* 1, chloroform), R_F 0.50 (t.l.c., ether–hexane, 1:1); ν_{max}^{film} 3440, 3000, 1640, 1580, 1460, 1380, 1220, 1070, 940, and 840 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 1.15–1.60 (m, 15 H, 2 CMe_2 and CHOH-*Me*), 2.30 (s, 3 H, Me-2), 2.6–2.8 (bs, OH), 3.8–4.5 (m, 4 H, H-2′,3′,4′,4′), 4.5–5.1 (m, 2 H, H-1′ and C*H*OH-Me), and 6.4 (s, 1 H, H-4).

Photo-oxygenation of **8a**. — *(a) In methanol.* Photo-oxygenation of **8a** (1.8 g, 5.5 mmol) in methanol (40 mL) was carried out under the general conditions for 30 min. An aliquot of the solution (40 mg) was concentrated *in vacuo* at room temperature. The residue was the hydroperoxide **11a** according to the ^{1}H-n.m.r. spectrum ($CDCl_3$): δ 1.55 (acetal Me-C), 3.3 (MeO), and 5.6–5.9 (vinylic H). Dimethyl sulphide (0.03 mL) was added to the n.m.r. solution. The ^{1}H-n.m.r. spectrum of the product indicated a mixture of Me_2SO [δ 2.52 (s, 6 H)] and the γ-diketone **10a** [δ 2.3 (s, 3 H, Me-CO) and 6.5 (m, 1 H, HC=).

The remainder of **11a** was treated with hydrazine (3 mL) for 3 days at room temperature. The solution was concentrated and the residue was treated several times with ethanol to remove hydrazine. The resulting syrup (1.1 g) was subjected to column chromatography (ether–hexane, 5:3) to give 6-(1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl)-4-(1-hydroxyethyl)-3-methylpyridazine (**12a**; 370 mg, 20%), $[\alpha]_D^{20}$ +5° (*c* 1, chloroform); ν_{max}^{film} 3350, 3000, 1605, 1375, 1220, 1150, 1070, 875, and 840 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 1.2, 1.3, 1.4, and 1.5 (3 s and 1 d, 15 H, 2 CMe_2 and *Me*-CHOH), 2.6 (s, 3 H, Me-3), 3.9–4.5 (m, 5 H, 1 H, exchangeable with D_2O), 4.9–5.3 (m, 2 H), and 7.85 (s, 1 H, pyridazine H-5).

(b) In acetone. Photo-oxygenation of **8a** (1.58 g, 4.8 mmol) in acetone (30 mL) was carried out for 30 min as in (*a*). An aliquot of the solution was concentrated *in vacuo* at room temperature. The residue was the *endo*-peroxide **9a** according to the ^{1}H-n.m.r. spectrum [$(CD_3)_2CO$]: δ 6.65 (bs, 1 H, vinylic H) and 1.8 (s, 3 H, Me-C$<^{OC}_{O}$).

The rearrangement **9a** → **14a** occurred during 12 h, as shown by the gradual appearance of signals at δ 6.3 (bs, 1 H, HC=) and 2.35 (s, 3 H, Me-CO). The main bulk of the solution was kept at room temperature for 24 h and then concentrated to afford a syrup which, after purification by column chromatography (ether), gave 1,2:3,4-di-*O*-isopropylidene-D-*arabino*-tetritol-1-yl 3-(1-hydroxyethyl)-4-oxopent-2-enoate (**14a**; 1.62 g, 93%), $[\alpha]_D^{20}$ +33° (*c* 1, acetone); ν_{max}^{film} 3400, 3000, 1750, 1660, 1380, 1170, 1080, and 850 cm^{-1}. ^{1}H-N.m.r. data [$(CD_3)_2CO$]: δ 1.3, 1.4, and 1.5 (3 s, 15 H, 2 CMe_2 and *Me*-CHOH), 2.35 (s, 3 H, Me-CO), 2.9 (bs, 1 H exchangeable with D_2O), 3.9–4.9 (bs, 5 H), 6.0 (s, 1 H), and 6.3 (bs, 1 H, HC=).

Acid hydrolysis of **12a**. — A solution of **12a** (180 mg, 0.53 mmol) in water containing trifluoroacetic acid (0.2 mL) was kept at room temperature for 24 h, and then concentrated. A solution of the residue in acetone was neutralised (K_2CO_3), filtered, and concentrated, and the residue (140 mg) was crystallised in ethyl acetate to give 6-(D-*arabino*-tetritol-1-yl)-4-(1-hydroxyethyl)-3-methylpyridazine (**13d**; 30 mg, 22%), m.p. 168–170°, $[\alpha]_D^{20}$ −75° (*c* 1, methyl sulfoxide); ν_{max}^{KBr} 3400,

1610, 1420, 1150, 1090, 1040, and 890 cm^{-1}. ^{1}H-N.m.r. data [$(CD_3)_2SO$, D_2O]: δ 1.45 (d, 3 H, *J* 6 Hz, *Me*-CHOH), 2.7 (s, 3 H, Me-3), 3.7–4.7 (m, 4 H), 5.2 (q, 1 H), 5.5 (bs, 1 H), and 8.15 (bs, 1 H, pyridazine H-5).

Anal. Calc. for $C_{11}H_{18}N_2O_5$: C, 51.13; H, 7.02; N, 10.83. Found: C, 50.73; H, 7.08; N, 10.30.

Acid hydrolysis of **14a**. — A solution of **14a** (1.4 g, 3.9 mmol) in CCl_4 (10 mL) was shaken for 16 h with a solution of trifluoroacetic acid (1 mL) in water (5 mL). The aqueous layer was extracted several times with ethyl acetate, and the combined extracts were dried (Na_2SO_4) and concentrated. The residue was treated several times with methanol to remove trifluoroacetic acid, yielding 4-(1-hydroxyethyl)-5-methoxy-5-methyl-2-oxo-2,5-dihydrofuran (**15a**; 280 mg, 42%) as a colorless syrup, R_F 0.46 (t.l.c., ether); ν_{max}^{film} 3500, 3000, 1780, 1660, 1390, 1200, 1100, 940, and 880 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 1.50 (d, 3 H, *J* 6 Hz, *Me*-CHOH), 1.70 (s, 3 H, acetal Me-C), 3.25 (s, 3 H, OMe), 3.70 (bs, 1 H, exchangeable with D_2O), 4.3–4.85 (m, C*H*OH-Me), and 6.10 (s, 1 H, HC=).

From the aqueous layer, the osazone of D-erythrose was isolated (500 mg, 45%; m.p. 162–164°) after reaction with phenylhydrazine[5].

*Photo-oxygenation of 2-methyl-5-(1,2,3,4-tetra-*O*-acetyl-*D*-arabino-tetritol-1-yl)-3-furoic acid* (**8b**). — Photo-oxygenation of a solution of **8b** (1 g, 2.4 mmol) in methanol (40 mL) was carried out for 30 min by the general method. An aliquot (4 mL) was then concentrated *in vacuo* at room temperature. The residue was the *endo*-peroxide **9b** according to the ^{1}H-n.m.r. spectrum ($CDCl_3$): δ 9.90 (bs, 1 H, COOH), 7.18 (s, 1 H, vinylic H), and 1.99 (s, 3 H, ME-C$<^{OO}_{O}$).

The remainder of the solution was treated with dimethyl sulphide (1 mL), and the solution was concentrated *in vacuo*. The resulting syrup was purified by column chromatography (acetone–hexane, 1:2), to give D-*arabino*-6,7,8,9-tetraacetoxy-4-methoxynonane-2,5-dione (**16b**; 0.5 g, 56%) as a mixture of two diastereomers. Fractional crystallisation gave one diastereomer (100 mg), m.p. 112–113°, $[\alpha]_D^{20}$ +89° (*c* 1, chloroform); ν_{max}^{KBr} 2950, 1745, 1705, 1370, 1225, 1210, 1035, and 965 cm^{-1}. N.m.r. data (80 MHz, $CDCl_3$): ^{1}H, δ 2.07, 2.09, 2.16, and 2.19 (4 s, 15 H, 4 OCOMe and COMe), 2.84 (d, 2 H, *J* 5.6 Hz, H-3,3), 3.54 (s, 3 H, OMe), 4.21–4.30 (m, 2 H, H-9,9), 4.40 (t, 1 H, *J* 5.6 Hz, H-4), 5.16–5.36 (m, 1 H, H-8), and 5.69–5.86 (m, 2 H, H-6,7); ^{13}C, δ 20.18, 20.37, 20.59 (acetate Me), 30.26 (C-1), 40.59 (C-3), 58.28 (OMe), 61.66 (C-9), 67.72 (C-8), 67.89 (C-7), 68.42 (C-6), 80.77 (C-4), 169.43, 169.72, 169.83, 170.24 (acetate CO), 203.56 (C-5), and 204.61 (C-2).

Anal. Calc. for $C_{16}H_{26}O_{11}$: C, 51.66; H, 6.26. Found: C, 51.67; H, 6.22.

In a non-repetitive experiment in chloroform, the diketone **10b** was isolated (74%), m.p. 93–94°, $[\alpha]_D^{20}$ +43.5° (*c* 1, chloroform); ν_{max}^{KBr} 3040, 1755, 1695, 1370, and 1225 cm^{-1}. ^{1}H-N.m.r. data ($CDCl_3$): δ 2.10, 2.12, 2.14, and 2.25 (4 s, 12 H, 4 OCOMe), 2.37 (s, 3 H, COMe), 4.17–4.27 (m, 2 H, H-9,9), 5.15–5.71 (m, 3 H, H-6,7,8), and 6.95 (s, 2 H, H-3,4), which was transformed into **12c** by condensation with hydrazine in methanol.

*6-(*D-arabino-*Tetritol-1-yl)-3-methylpyridazine* (**12c**). — A solution of **16b** (0.1 g, 0.24 mmol) and hydrazine (0.5 g, 15.6 mmol) in ethanol (5 mL) was kept at room temperature for 72 h and then concentrated *in vacuo*, and the resulting syrup was treated with acetic acid to remove hydrazine. The solution was concentrated *in vacuo* and the resulting syrup was crystallised from ethanol to yield **12c** (0.04 g, 78%), m.p. 152–153°, $[\alpha]_D^{20}$ −57.5° (*c* 1, water); ν_{max}^{KBr} 3400, 1595, 1455, 1085, 1045, 950, and 890 cm^{-1}. ^{1}H-N.m.r. data [$(CD_3)_2SO$]: δ 2.62 (s, 3 H, Me-3), 3.45–3.80 (m, 4 H, H-2′,3′,4′,4′), 4.20–4.75 (m, 3 H, exchangeable with D_2O), 5.00–5.45 (m, 2 H, 1 H exchangeable with D_2O, H-1′ and OH), 7.51 (d, 1 H, *J* 8.4 Hz, H-4), and 7.62 (d, 1 H, *J* 8.4 Hz, H-5).

Anal. Calc. for $C_9H_{14}N_2O_4 \cdot 0.5\ H_2O$: C, 48.42; H, 6.77; N, 12.55. Found: C, 48.12, 47.99; H, 6.85, 6.87; N, 12.36.

REFERENCES

1 F. J. LOPEZ APARICIO, J. A. LOPEZ SASTRE, J. ISAC GARCIA, AND R. ROBLES DIAZ, *Carbohydr. Res.*, 132 (1984) 19–27.

2 F. GARCIA GONZALEZ, F. J. LOPEZ APARICIO, AND A. VAZQUEZ RONCERO, *An. R. Soc. Esp. Fis. Quim., Ser. B*, 45 (1949) 1539–1564; F. J. LOPEZ APARACIO, M. T. PLAZA LOPEZ-ESPINOSA, AND R. ROBLES DIAZ, *An. Quim.*, in press.

3 J.-L. IMBACH, J. L BARASCUT, B. L. KAM, B. RAYNER, C. TAMBY, AND C. TAPIERO, *J. Heterocycl. Chem.*, 10 (1973) 1069–1070; J.-L. IMBACH, J. L. BARASCUT, B. L. KAM, AND C. TAPIERO, *Tetrahedron Lett.*, (1974) 129–130; M. MACCOSS, M. J. ROBINS, B. RAYNER, AND J.-L. IMBACH, *Carbohydr. Res.*, 59 (1977) 575–579.

4 E. S. WEST, *J. Biol Chem.*, 74 (1927) 561–589.

5 A. S. PERLIN, *Methods Carbohydr. Chem.*, 1 (1962) 64–66.

6 F. FARIÑA, M. V. MARTIN, AND M. C. PAREDES, *An. Quim., Ser. C*, 77 (1981) 213–217.